IN THE SPECIFICATION

Please replace the description of Figure 1B at page 3, lines 17-18, with the following re-written figure description:

B1 -- Figure 1B shows the DNA sequence encoding and the amino acid sequence of murine endostatin, to which is attached a mouse Ig-K leader sequence (SEQ ID NO:1 and SEQ ID NO:2); --

Please replace the description of Figure 5 at page 4, lines 12-26, with the following re-written figure description:

-- Figure 5 shows adenoviral-mediated expression and secretion of murine endostatin in S8 cells. The mEndo (lane 2) and NulI (lane 3) supernatant proteins were analyzed by SDS-PAGE. Each 60 μg supernatant protein was analyzed on 4 to 12% linear gradient pre-casted gel. The protein standard marker was run on lane 1. The gel was stained with Gelcode Blue stain reagent B2 to visualize the protein bands. As indicated, the expected murine endostatin protein band around 20 Kd (marked by arrow) was generated only from Av3mEndo but not from the control Av3NulI. After being transferred to a PVDF membrane from a duplicate SDS-PAGE, the 20 Kd protein band was excised from an immoblin membrane blot and subjected to N-terminal protein sequencing analysis. The determined protein sequence (SEQ ID NO:3) is shown at the bottom with arrows marked as the beginning of the N-termini of two major secreted proteins, 80% containing additional amino acid residues of DAA, and 20% containing residue A from murine Ig-K signal peptide. The results demonstrated that S8 cells transduced with Av3mEndo expressed and secreted murine endostatin after it was processed from murine Ig-K signal peptide; --

Please replace the description of Figure 9 at page 5, lines 18-27, with the following re-written figure description:

B3 -- Figure 9 depicts the results of a B16F10 mouse lung metastasis study. C57BL/6J mice were treated with Av3mEndo (n=20), Av3NulI (n=20), or HBSS (n=12) by tail vein injection at $2x10^{11}$ particles per mouse. Two days later, lung metastasis was established by tail vein injection of B16F10 cells at $5x10^4$ cells per mouse. 14 days after tumor implantation, the study was

B3 ended. Blood levels of murine endostatin were determined. Surface lung metastasis was determined. Liver transduction (copy number per hepatocyte) was correlated to blood endostatin levels. --

Please replace the description of Figure 12B at page 6, lines 12-14, with the following re-written figure description:

B4 -- Figure 12B shows the DNA sequence encoding human endostatin, and the amino acid sequence of human endostatin, to which is attached a human BM40 basement membrane protein leader sequence (SEQ ID NO:4 and SEQ ID NO:5). --

Please replace the description of Figure 13 at page 6, lines 15-16, with the following re-written figure description:

B5 -- Figure 13 shows adenoviral-mediated expression and secretion of human endostatin in S8 cells. The determined protein sequence (SEQ ID NO:6) is shown at the bottom of Figure 13 with arrows marked at the beginning of the N-termini of three major secreted proteins, 50% containing the additional amino acid residues APQQEALA (SEQ ID NO:7), 25% containing residues LA, and 25% containing no residues from human BM40 basement protein signal peptide. --

Please replace the paragraph at page 17, lines 9-18, with the following re-written paragraph:

B6 -- The mouse endostatin cDNA was PCR amplified from mouse collagen XVIII clone ID #748987 from GenomeSystems, Inc. with the primers of SEQ ID NO:8 and SEQ ID NO:9: 5'-ACT GGT GAC GCG GCC CAT ACT CAT CAG GAC TTT CAG CC-3' and 5'-AAG GGC TAT CGA TCT AGC TGG CAG AGG CCT AT-3' (598 bp F1 fragment). The mouse Ig-kappa leader was PCR amplified from pSecTag2 (Invitrogen) with the primers of SEQ ID NO:10 and SEQ ID NO:11: 5'-CAC TGC TTA CTG GCT TAT CG-3' and 5'-CTG ATG AGT ATG GGC CGC ACC AGT GG-3' (147 bp F2 fragment). PCR was carried out with Pfu DNA polymerase (Stratagene) for 35 cycles in the following conditions: 95°C hot start for 3 min., 95°C denaturation for 1 min, 55°C annealing for 1 min, and 72°C extension for 2 min. The DNA fragments were gel purified. --

Please replace the paragraph at page 17, lines 19-27, with the following re-written paragraph:

-- The sig-mEndo chimeric DNA (718 bp) was generated by PCR splice overlap extension (Horton, *et al.*, Biotechniques, Vol. 8, pgs. 528-535 (1990)) with F1 and F2 DNA fragments generated above as templates to assemble mouse Ig-kappa leader sequence and murine endostatin cDNA. PCR was carried out with the primers of SEQ ID NO:8 and SEQ ID NO:12: 5'-ACT GGT GAC GCG GCC CAT ACT CAT CAG GAC TTT CAG CC-3' and 5'-CTG ATG AGT ATG GGC CGC GTC ACC AGT GG-3' using Pfu DNA polymerse (Stratagene, LaJolla, California). PCR was run for 35 cycles in the following conditions: 95°C hot start for 3 min., 95°C denaturation for 1 min, 60°C annealing for 1 min, and 72°C extension for 2 min. --

Please replace the paragraph at page 23, lines 3-15, with the following re-written paragraph:

-- Murine endostatin cDNA was PCR generated from the C-terminus of mouse α1(XVIII) collagen clone ID #748987 from GenomeSystems. The cDNA was assembled with murine Ig-kappa leader to generate sig-mEndo chimeric for the secretion of murine endostatin protein by PCR splice overlap extension (Horton, *et al.*, 1990). The sig-mEndo chimeric DNA was cloned into the Nhe1 and ClaI sites of the adenoviral shuttle plasmid, pAvF91xr to create pAvmEndoLxr (Fig. 1A). The entire sig-mEndo chimeric sequence was confirmed by auto sequencing analysis. The consensus sequence (SEQ ID NO:1) and derived protein sequence (SEQ ID NO:2) are shown in Fig 1B. The adenoviral vector encoding sig-mEndo chimeric was generated by the "Quick Cre/Lox 2 plasmid system" in 293 cells by transient transfection with pcmvE2a, pCre, pSQ3 and pAv3mEndoLx through Cre/Lox mediated recombination. The generated vector was RCA negative. The correct genome structure of generated Av3mEndo vector was confirmed by restriction digests and Southern Blot analysis (Fig. 3A and B). --

Please replace the paragraph at page 29, lines 4-13, with the following re-written paragraph:

-- The B16F10 lung metastasis model was established in C57B16/J mice by tail vein injection of 5 x 10^4 cells per mouse. Two days before tumor implantation, the mice were treated

with Av3mEndo vector by tail vein injection at 2 x 10^{11} particles per mouse. Controls were carried out with either equal volume of HBSS or the equal amount of Av3NulI vector. Fourteen days post tumor implantation, blood was collected from all animals and analyzed by mEndo ELISA. The mice treated with Av3mEndo vectors all demonstrated higher level of murine endostatin at an average of 708 ± 435 ng/m1. In contrast, the control mice treated with HBSS and Av3NulI only showed the endogenous level of murine endostatin at an average of 50 ± 15 and 56 ± 19 ng/m1, respectively. --

Please replace the paragraph extending from page 29, line 19, to page 30, line 5, with the following re-written paragraph:

-- Lung surface metastasis was determined in all mice. The control mice treated with HBSS showed the highest number of lung metastases at an average of 109 ± 65 number of lung metastases/mouse. Mice treated with Av3mEndo vectors demonstrated the reduction of lung metastases to the average of 36 ± 18 number of lung metastases/mouse (33% relative to HBSS control). However, mice treated with Av3NulI vectors also demonstrated the reduction of lung metastases to the average of 42 ± 28 number of lung metastases/mouse (39% relative HBSS control). This indicated that the majority of anti-metastasis effect (61%) was caused by Av3 backbone vector and some reduction (6%) was caused by murine endostatin secretion. The current study does prove that Av3mEndo expressed and secreted functional murine endostatin was demonstrated in vitro. Systemic administration of Av3mEndo demonstrated sustained blood level of endostatin as demonstrated on day 16 post vector injection. The results support that anti-angiogenesis gene therapy of angiogenic inhibitor gene delivery may provide a means to reduce lung metastasis. --

Please replace the paragraph extending from page 31, line 21, to page 32, line 13, with the following re-written paragraph:

-- The human endostatin cDNA was PCR amplified from the cDNA of human α1 (XVIII) collagen. The human liver cDNA was generated from human liver poly A RNA (Clonetech, Palo Alto, CA) by reverse transcriptase polymerase chain reaction (RT- PCR). The reverse transcription was carried out with the primer of 5'-TTT TTT TTT CAG TGT AAA AGG TC-3'

(SEQ ID NO:13) using the Perkin Elmer RT-PCR kit (Perkin Elmer Applied Biosystems, Foster City, CA) for 1 cycle in the following conditions: room temperature for 10 min, 42°C reverse transcribing for 3 min, 99°C denaturation for 5 min, 5°C cooling for 5 min, and hold at 4°C until the cDNA was ethanol precipitated and resuspended. The 790 bp human endostatin cDNA fragment was PCR amplified from the prepared cDNA with the primers of SEQ ID NO:14 and SEQ ID NO:15: 5'-CAG ATG ACA TCC TGG CCA G-3' and 5'-CTA TAC AGG AAA GTA TGG CAG C-3'. PCR was carried out for 35 cycles in the following condition: 95°C hot start for 3 min, 80°C for 3 min followed by the addition of Pfu DNA polymerase (Stratagene, La Jolla, CA), 95°C denaturation for 1 min, 55°C annealing for 1 min, and 72°C extension for 3 min. The 790 bp human endostatin cDNA fragment was gel purified and reamplified as described except using the annealing temperature of 58°C. The 790 bp human endostatin cDNA fragment was gel purified and cloned into PCR-Script Amp SK^+ using PCR-Script Cloning Kits (Stratagene) according to the manufacturer's procedure to generate pcrhend 1. The human endostatin cDNA region of the pcrhend 1 plasmid was confirmed with the direct sequencing analysis by Gene Therapy Core Technologies Molecular Core Laboratory at Genetic Therapy, Inc. Gaithersburg, MD. --

Please replace the paragraph extending from page 32, line 14, to page 33, line 4, with the following re-written paragraph:

-- The human endostatin cDNA fragment was assembled with human BM40 basement protein leader according to the following procedure. The BM40 basement protein leader was generated by annealing 2 pieces of synthesized oligonucleotides, 5'-GCC AAG CTT CCA TGA GGG CCT GGA TCT TCT TTC TCC TTT GCC TGG CCG GGA GGG CTC TGG CAG CCC CTC AGC AAG AAG CGC TCG CTC ACA GCC ACC GCG ACT TCC AGC CGG TGC TCC A-3' (sense; SEQ ID NO:16), and 5'-CCA GGT GGA GCA CCG GCT GGA AGT CGC GGT GGC TGT GAG CGA GCG CTT CTT GCT GAG GGG CTG CCA GAG CCC TCC CGG CCA GGC AAA GGA GAA AGA AGA TCC AGG CCC TCA TGG AAG CTT GGC-3' (antisense; SEQ ID NO:17) followed by Hind III and Sex A1 digestion. Th digested BM40 basement protein leader was cloned into Hind III and Sex A1 sites of pcrhend 1 to generate pBmpcrhen plasmid. The entire sig-hEndo region of the pBmpcrhen plasmid was confirmed with the direct

sequencing analysis by Gene Therapy Core Technologies Molecular Core Laboratory at Genetic Therapy, Inc. The adenovial shuttle plasmid pAV1bmhend1x was generated by substitution of the Factor IX (F9) containing sequence with the sig-Endo containing sequence in pAvF9Lxr adenoviral shuttle plasmid in the following procedure. An 800 bp fragment containing sig-hEndo sequence was generated from pBmpcrhen by SacI digestion followed by Klenow fill in and Sal I digestion. The pAvF9Lxr plasmid was digested with Bam HI restriction enzyme followed by Klenow fill in and digested with Sal I restriction enzyme to remove F9 containing sequences. The two digested fragments were gel purified and ligated to generate pAV1bmhendlx. (Figure 12A). --

Please replace the paragraph at page 34, lines 8-19, with the following re-written paragraph:

-- Human endostatin cDNA was RT-PCR generated from the C-terminus of cDNA of human α1 (XVIII) collagen from human liver poly A RNA. The human BM40 basement protein leader was generated from two pieces of synthesized oligonucleotides. The annealed human BM40 basement protein leader was cloned 5' of the human endostatin cDNA to generate sig-hEndo chimeric protein for the secretion of human endostatin protein. The sig-hEndo chimeric DNA was cloned into the adenoviral shuttle plasmid, pAvF9lxr to create pAV1bmhendlx (Fig. 12A). The entire sig-hEndo chimeric sequence was confirmed by auto sequencing analysis. The consensus sequence (SEQ ID NO:4) and derived protein sequence (SEQ ID NO:5) are shown in Fig 12B. The adenoviral vector encoding sig-hEndo chimeric was generated by the "Quick Cre/Lox 2 plasmid system" in S8 cells by transient transfection with pCre, pSQ3, and pAV1bmhendlx through Cre/Lox mediated recombination. --

Please replace the paragraph extending from page 34, line 21, to page 35, line 12, with the following re-written paragraph:

-- Av3bmhendlx mediated human endostatin expression and secretion was characterized in vector transduced S8 cells. As shown in Figure 13, the supernatant protein of Av3bmhendlx, i.e., human endostatin, was analyzed by SDS-PAGE (lanes 1-8 and 10). Each 20 μg of supernatant protein was analyzed on 4 to 12% linear gradient precasted gel. The protein standard marker was

run on lane 9. The SDS-PAGE was transferred to a polyvinylidene fluoride membrane. The membrane was stained with Coomassie blue R-250. The 20 kDa protein bands, corresponding to the correct size of human endostatin, were excised from a membrane blot and subjected to N-terminal protein sequencing analysis. The determined protein sequence (SEQ ID NO:6) is shown at the bottom of Figure 13 with arrows marked at the beginning of the N-termini of three major secreted proteins, 50% containing the additional amino acid residues APQQEALA (SEQ ID NO:7), 25% containing residues LA, and 25% containing no residues from human BM40 basement protein signal peptide. The 20 kDa protein was not shown in the supernatant protein from Av3NullI cells. (Figure 5). The results demonstrated that S8 cells transduced with Av3bmhendlx expressed and secreted human endostatin after it was processed from human BM40 basement protein signal peptide. --

Please insert the enclosed Sequence Listing, pages 1-8, into the specification.